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PATENT
USSN 09/677,672
574313-3160

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Audonnet et al.
Serial No.	:	09/677,672
For	:	ADJUVANT-CONTAINING DNA VACCINES
Filed	:	October 2, 2000
Examiner	:	Dave Nguyen
Art Unit	:	1632

745 Fifth Avenue, New York, NY 10151

EXPEDITED PROCEDURE
RESPONSE AFTER FINAL ACTION
UNDER 37 C.F.R. §1.116

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Date of Deposit: November 12, 2004

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COMMUNICATION FORWARDING DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Further to the Amendment filed October 25, 2004, and in response to the Advisory Action mailed November 8, 2004, enclosed herewith is an executed copy of the Declaration under 37 C.F.R. §1.132 by Dr. Jean-Christophe Audonnet. The unsigned Declaration of Dr. Audonnet originally accompanied the October 25, 2004 Amendment.

The Examiner is thanked for the indication in the Advisory Action that the rejection under 35 U.S.C. §102(e) had been withdrawn. Applicants respectfully request that the Examiner

review the arguments of the October 25, 2004 Office Action in regards to the §103 rejection, especially in view of the executed Declaration filed herewith.

Specifically, claims 1, 5, 6, 10, 13 and 19 remain rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Davis (U.S. 2002/0164341), Olsen (US 2001/0007860) or Crabb (U.S. 5,922,237) taken with any of Miles, Inc. (EP 0 532 833 A1), Lowell (WO 95/11700), Chavez, Gicquel (US 2001/0024653) or Wasmoen (US 5,989,562). The rejection is respectfully traversed.

It is respectfully submitted that the accompanying executed Declaration by the first named inventor, Dr. Jean-Christophe Audonnet overcomes the rejection under §103.

Dr. Audonnet declares that the experiment showing the superiority of a DNA vaccine comprising an antigen of rhinopheumonia virus and carbopol when tested against a DNA vaccine that lacks carbopol was performed under his direction, supervision and control in the ordinary course of business. Furthermore, as shown in the data accompanying the Declaration as Exhibit 2, the results from EHV-1 indicate that the general trend was that animals vaccinated with naked DNA and Carbopol® had higher levels of neutralizing antibodies and lower virus excretion than those vaccinated with naked DNA only. And, animals vaccinated with naked DNA and Carbopol® had a lower percentage of positive viral isolation by the end of the 21 day period. Additionally, Dr. Audonnet declares that a lowering of the virus excretion levels is especially important in animals such as equines that are stabled together and graze together, thereby having a greater chance of being exposed to EHV by the nasal droplets or mucus of an infected equine.

As shown in the accompanying Declaration, and as declared by Dr. Audonnet, the addition of Carbopol® to the naked DNA vaccine provides enhanced results that are not evident, and would not be inferred, from any of the documents cited in the Office Action.

As the documents cited in the Office Action do not teach or suggest that an incorporation of Carbopol® as an adjuvant in a naked DNA vaccine composition will enhance its vaccination effect, the Section 103 rejections cannot stand.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §103 are respectfully requested.

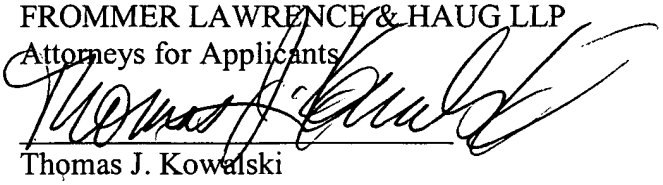
CONCLUSION

In view of the remarks and enclosures herewith, Applicants have addressed and overcome all rejections of the application set forth in the Office Action, and the present application is in condition for allowance.

Thus, early and favorable reconsideration and withdrawal of the rejections of the application as set forth in the Office Action, and, prompt issuance of a Notice of Allowance, or an interview with supervisory review, at an early date, with a view towards reaching agreement on allowable subject matter, are earnestly solicited.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP
Attorneys for Applicants

By: 

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants		AUDONNET et al.
Serial No.	:	09/677,672
Filing Date	:	October 2, 2000
For	:	ADJUVANT-CONTAINING DNA VECTORS
Examiner	:	Dave Nguyen
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Charles Jackson
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(Signature of person mailing paper or fee)

DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Dr. Jean-Christophe Audonnet, declare and state that:

1. I make this declaration in connection with U.S. Application Serial No. 09/677,672. I am a co-inventor of this application and am familiar with its prosecution history, particularly as it pertains to the Final Office Action mailed April 23, 2004 and the rejection under 35 U.S.C. §103(a) of claims 1- as allegedly being unpatentable over any of Davis, Olsen or Crabb taken with any of Miles Inc., Lowell, Chavez, Gicquel or Wasmoen.

2. I am a citizen of France. As indicated on my attached *Curriculum vitiae* (Exhibit 1), I received a veterinary degree from Ecole Nationale Vétérinaire d'Alfort in 1980, a master's degree in molecular biology and genetics from University Montpellier in 1984, and a doctorate in molecular biology from Lyon University in 1989. I have also received a Certificate of Compared and Animal Immunology, a Certificate of Immunology and a degree in general virology. I have been employed by Merial, the assignee of this application, since September, 1997, and have served as Director of Molecular Biology and Immunology since May, 2001. From June, 1993 to September, 1997, I was employed as Head of the Molecular Biology and Genetic Recombination Units by Merial's predecessor company, Rhône Mérieux Lyon. In view of my education and experience, I consider myself to be an expert in the field to which this application pertains.

3. The April 23, 2004 Office Action alleges that the combination of any of Davis, Olsen or Crabb taken with any of Miles Inc., Lowell, Chavez, Gicquel or Wasmoen renders the instant invention obvious. The Office Action argues that Davis, Olsen and Crabb teach DNA vaccines, and that Miles Inc., Lowell, Chavez, Gicquel and Wasmoel teach the use of adjuvants including Carbopol®. All of Miles Inc., Lowell, Chavez, Gicquel and Wasmoel teach the use of these adjuvants in classical vaccines—vaccines that upon administration present an epitope or antigen to the immune system—or RNA vaccines, in which an entire or deleted genome is administered. In contrast, the presently pending claims relate to a DNA vaccine comprising (i) a naked DNA plasmid containing and expressing *in vivo* a polynucleotide encoding an antigenic polypeptide, wherein the antigenic polypeptide comprises an antigen of equine rhinopheumonia virus; and (ii) at least one adjuvant comprising carbopol.

4. In my expert opinion, one of skill in the art would not have applied the adjuvants used in Miles Inc., Lowell, Chavez, Gicquel and Wasmoel to the DNA vaccines of Davis, Olsen or Crabb with any expectation of success. Indeed, it was surprising and unexpected that the adjuvant of the instant claims functions to enhance immunogenicity of that which is expressed by the DNA vaccine, in this case, equine rhinopheumonia virus; and, there is no motivation from the cited documents to employ the adjuvants of the instant claims to DNA plasmid vaccines.

5. Attached as Exhibit 2 is a graph showing results obtained during experiments carried out under my direct knowledge, supervision and control in the ordinary course of business. These results were obtained by vaccinating horses with naked DNA containing and

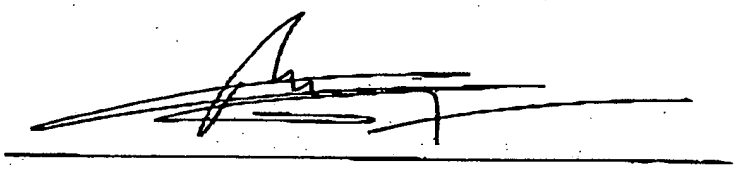
expressing *in vivo* a polynucleotide encoding an antigenic polypeptide of EHV-1, both with and without the addition of Carbopol®. The graphs depicting the results from EHV-1 indicate that the general trend was that animals vaccinated with naked DNA and Carbopol® had higher levels of neutralizing antibodies and lower virus excretion than those vaccinated with naked DNA only. And, animals vaccinated with naked DNA and Carbopol® had a lower percentage of positive viral isolation by the end of the 21 day period.

6. The lower viral excretion resulting from the DNA and Carbopol® vaccine is especially important because equines tend to be housed in stables, and allowed to graze in large numbers, thereby placing individual animals in direct contact and/or close proximity with other equines, which significantly increases the chances of being exposed to EHV through the nasal droplets or mucus of infected equines. Consequently, the lowering of viral excretion levels by the presence of Carbopol® in the vaccine is of great importance.

7. In view of the foregoing, it is my opinion, as one of skill in the art, that there could have been no reasonable expectation of success for combining the use of adjuvants as taught by Miles Inc., Lowell, Chavez, Gicquel and Wasmoel with the DNA vaccines of Davis, Olsen or Crabb. Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) are requested.

8. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. These statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: NOVEMBER 3, 2004



Jean-Christophe Francis Audonnet, Ph.D.

CONFIDENTIAL
Summary Curriculum Vitae

Name: AUDONNET Jean-Christophe **Unit:** Biological Research

Location: Lyon Gerland

Date of birth: 01/08/57 (dd/mm/yy) **Date of entry:** 01/10/88 (dd/mm/yy)

CURRENT POSITION & MAIN RESPONSIBILITIES

Job Title: Director, Molecular Biology and Immunology, Discovery Research

Main Responsibilities:

- Global management of the molecular biology research projects conducted by Merial (internal and external (collaborations) projects
- Global management of the activities of the Immunology department (internal and external projects)
- Technical supervision of the molecular biology projects conducted by the Aventis Pasteur / Merial veterinary team (located in Toronto, Ontario, Canada)
- Maintaining Merial's high level of expertise in the molecular biology and immunology areas in order to ensure through reviews of external research proposals
- Proposition and definition of the future research programs involving molecular biology techniques or expertise in immunology

Direct reports : head of molecular biology / bacteriology department (Merial Lyon), head of immunology department (Merial Lyon), 1 secretary, team leader of the vet team at Virogenetics (USA/Canada)
3 teams of 6-8 people each + 1 secretary specific for the Discovery Lyon Direction
Total of 17 people in Lyon + 1 in USA/Canada under direct or indirect supervision for performances assessment

- Member of the "Ethical Committee" of the Lyon National Veterinary School (since 1998)
- President of the "Ethical Committee" (Institutional Care and Use Committee) for MERIAL Lyon Gerland since January 1995 (this "function" is independent of the current position)

SUMMARY OF PREVIOUS PROFESSIONAL EXPERIENCE & KEY ACHIEVEMENTS

June 2002 – present : see above (integration of the bacteriology staff into the global activities and supervision).

May 2001 – June 2002 : Director, Molecular Biology and Immunology. Management and coordination of all Molecular Biology and Immunology activities (internal and external) for Merial.

October 2000 – April 2001 : Director (acting) Bio-Analytical Department, BioDevelopment Management and coordination of Merial global analytical activities in Lyon Gerland (52 people, 7 labs) and Athens, Georgia USA (14 people, 3 labs). Building and organizing the international global team in the new R&D structure.

July 2000 – September 2000 : Director, Molecular Biology and Immunology, Discovery Research Supervision of all molecular biology research projects conducted by Merial, supervision of all activities of the Immunology department, technical supervision of the molecular biology projects conducted by the veterinary team of Aventis Pasteur / Merial (located in Toronto Ontario, Canada), proposals and definition of new research programs involving molecular biology and / or immunology expertises. Project leader for the evaluation of recombinant viruses (canarypox-derived vaccines, adenovirus-derived vaccines, herpesvirus-derived vaccines).

February 2000 – July 2000 : Associate Director, Molecular Biology and Immunology Department, Biological Research Merial Lyon. Technical supervision of the molecular biology research projects conducted by Merial, proposals and definition of the future research programs, supervision of the activities of the Immunology department, technical supervision of the molecular biology projects conducted by the veterinary team of Virogenetics (located in Albany NY, USA until June 00, and then in Toronto, Ontario Canada).

September 97 – January 2000 : Associate Director, Head of Molecular Biology Department. Merial Lyon. Technical supervision of 2 molecular biology units (6 people each) (Merial Lyon and Virogenetics). Supervision of internal and external molecular biology research projects conducted for Merial. Definition of future research programs in molecular biology.
1997 Rhône-Poulenc Prize for Research (for the HVT/IBDV project)
Direct supervision of 5 scientists + 2 technicians (Lyon) + 1 scientist (Virogenetics)

February 95 – September 97 : Head of the "Molecular Biology Unit" Rhône Mérieux Lyon. Direct supervision of 6 scientists and 1 technician). Project leader for the DNA vaccination research program. Supervision of veterinary research projects conducted at Virogenetics.
Direct supervision of 5 scientists + 1 technician (Lyon) + 1 scientist (Virogenetics)

June 93 – January 95 : Head of the "Genetic Recombination Unit" Rhône Mérieux Lyon.
Direct supervision of 4 scientists, 1 technician, and 1 graduate student)
Project leader for the Feline Infectious Peritonitis vaccine project
Project leader for the Infectious Bovine Rhinotracheitis vaccine project (Ibraxion)
Participation to the technical coordination of molecular biology external research projects

QUALIFICATIONS/PROFESSIONAL MEMBERSHIPS/TRAINING; LANGUAGES & DEGREE OF PROFICIENCY

1980 : DVM (Ecole Nationale Vétérinaire d'Alfort)
1981 : Certificate of Compared and Animal Immunology (Alfort, France)
1984 : Molecular Biology and Genetics degrees (Master's level) Univ. Montpellier ; Certificate of Immunology (Medical School University, Montpellier)
1985 : General Virology degree Institut Pasteur Paris
1989 : PhD degree (Molecular Biology) Lyon University
1995-96 : training in patents ; Centre Paul Roubier Lyon
1999 : Team management

Member of "Anciens Eleves de l'Ecole d'Alfort"
Member of "Société Française de Microbiologie" (SFM)
Member of "Association des Anciens Eleves de l'Institut Pasteur"

French (native)
English (fluent ; read, written and spoken) (3 years of work at Virogenetics Corp. Albany, NY, USA 1989-1992).
German : school level

SELECTED PUBLICATIONS AND PATENTS

Minke JM, Audonnet JC, Fischer L., "Equine viral vaccines: the past, present and future." Vet Res. 2004 Jul-Aug;35(4):425-43.

Minke JM, Siger L, Karaca K, Austgen L, Gordy P, Bowen R, Renshaw RW, Loosmore S, Audonnet JC, Nordgren B., "Recombinant canarypoxvirus vaccine carrying the prM/E genes of West Nile virus protects horses against a West Nile virus-mosquito challenge." Arch Virol Suppl. 2004(18):221-30.

Fischer L, Minke J, Dufay N, Baudu P, Audonnet JC., "Rabies DNA vaccine in the horse: strategies to improve serological responses." Vaccine. 2003 Nov 7;21(31):4593-6.

Poulet H, Brunet S, Boularand C, Guiot AL, Leroy V, Tartaglia J, Minke J, Audonnet JC, Desmettre P., "Efficacy of a canarypox virus-vectored vaccine against feline leukaemia." Vet Rec. 2003 Aug 2;153(5):141-5.

Fischer L, Barzu S, Andreoni C, Buisson N, Brun A, Audonnet JC., "DNA vaccination of neonate piglets in the face of maternal immunity induces humoral memory and protection against a virulent pseudorabies virus challenge." Vaccine. 2003 Apr 2;21(15):1732-41.

Fischer L, Tronel JP, Minke J, Barzu S, Baudu P, Audonnet JC., "Vaccination of puppies with a lipid-formulated plasmid vaccine protects against a severe canine distemper virus challenge." Vaccine. 2003 Mar 7;21(11-12):1099-102.

Laval F, Paillot R, Bollard S, Fischer L, Audonnet JC, Andreoni C, Juillard V., "Quantitative analysis of the antigen-specific IFNgamma+ T cell-mediated immune response in conventional outbred pigs: kinetics and duration of the DNA-induced IFNgamma+ CD8+ T cell response." Vet Immunol Immunopathol. 2002 Dec;90(3-4):191-201.

Fischer L, Tronel JP, Pardo-David C, Tanner P, Colombet G, Minke J, Audonnet JC., "Vaccination of puppies born to immune dams with a canine adenovirus-based vaccine protects against a canine distemper virus challenge." Vaccine. 2002 Oct 4;20(29-30):3485-97.

Paillot R, Laval F, Audonnet JC, Andreoni C, Juillard V., "Functional and phenotypic characterization of distinct porcine dendritic cells derived from peripheral blood monocytes." Immunology. 2001 Apr;102(4):396-404.

Bublot M, Laplace E, Audonnet JC., "Non-essential loci in the BamHI-I and -F fragments of the HVT FC126 genome." Acta Virol. 1999 Apr-Jun;43(2-3):181-5.

Somasundaram C, Takamatsu H, Andreoni C, Audonnet JC, Fischer L, Lefevre F, Charley B., "Enhanced protective response and immuno-adjuvant effects of porcine GM-CSF on DNA vaccination of pigs against Aujeszky's disease virus." Vet Immunol Immunopathol. 1999 Sep 20;70(3-4):277-87.

Darteil R, Bublot M, Laplace E, Bouquet JF, Audonnet JC, Riviere M., "Herpesvirus of turkey recombinant viruses expressing infectious bursal disease virus (IBDV) VP2 immunogen induce protection against an IBDV virulent challenge in chickens." Virology. 1995 Aug 20;211(2):481-90.

Corapi WV, Darteil RJ, Audonnet JC, Chappuis GE., "Localization of antigenic sites of the S glycoprotein of feline infectious peritonitis virus involved in neutralization and antibody-dependent enhancement." J Virol. 1995 May;69(5):2858-62.

Leung-Tack P, Audonnet JC, Riviere M., "The complete DNA sequence and the genetic organization of the short unique region (US) of the bovine herpesvirus type 1 (ST strain)." Virology. 1994 Mar;199(2):409-21.

Zelnik V, Darteil R, Audonnet JC, Smith GD, Riviere M, Pastorek J, Ross LJ., "The complete sequence and gene organization of the short unique region of herpesvirus of turkeys." J Gen Virol. 1993 Oct;74 (Pt 10):2151-62.

Tartaglia J, Perkus ME, Taylor J, Norton EK, Audonnet JC, Cox WI, Davis SW, van der Hoeven J, Meignier B, Riviere M., "NYVAC: a highly attenuated strain of vaccinia virus." Virology. 1992 May;188(1):217-32.

Audonnet JC, Winslow J, Allen G, Paoletti E., "Equine herpesvirus type 1 unique short fragment encodes glycoproteins with homology to herpes simplex virus type 1 gD, gI and gE." J Gen Virol. 1990 Dec;71 (Pt 12):2969-78.

6,713,068 Live recombined vaccines injected with adjuvant

6,586,412 Polynucleotide vaccine formula against canine pathologies, in particular respiratory and digestive pathologies

6,576,243 Polynucleotide vaccine formula against porcine reproductive and respiratory pathologies

6,558,674 Polynucleotide vaccine formulation against pathologies of the horse

6,541,458 Feline calicivirus genes and vaccines in particular recombinant vaccines

6,517,843 Reduction of porcine circovirus-2 viral load with inactivated PCV-2

6,464,984 Avian polynucleotide vaccine formula

6,387,376 Recombinant vaccine containing feline herpes virus type 1 particularly for treating feline infectious peritonitis

6,376,473 Polynucleotide vaccine formula in particular against bovine respiratory pathology

6,358,512 Feline infectious peritonitis vaccine

6,348,196 Feline polynucleotide vaccine formula

6,306,400 Avian recombinant live vaccine using, as vector, the avian infectious laryngotracheitis

6,228,846 Polynucleotide vaccine formula against canine pathologies

6,224,878 Mutants and vaccines of the infectious bovine rhinotracheitis virus

6,221,362 Avian polynucleotide formula

6,217,883 Porcine circovirus and paravovirus vaccine

6,207,166 Polynucleotide formulation against pathologies of the horse

6,207,165 Polynucleotide formula against porcine reproductive and respiratory pathologies

6,159,477 Canine herpesvirus based recombinant live vaccine, in particular against canine distemper, rabies or the parainfluenza 2 virus

6,153,199	Avian recombinant live vaccine using, as vector, the avian infectious laryngotracheitis virus
6,096,535	Feline infectious peritonitis vaccine
6,074,649	Recombinant composition containing feline herpes virus type 1, particularly for treating feline infectious peritonitis
6,045,803	Live recombinant avian vaccine using an avian herpesvirus as vector
6,033,670	Recombinant live avian vaccine, using as vector the avian infectious laryngotracheitis virus

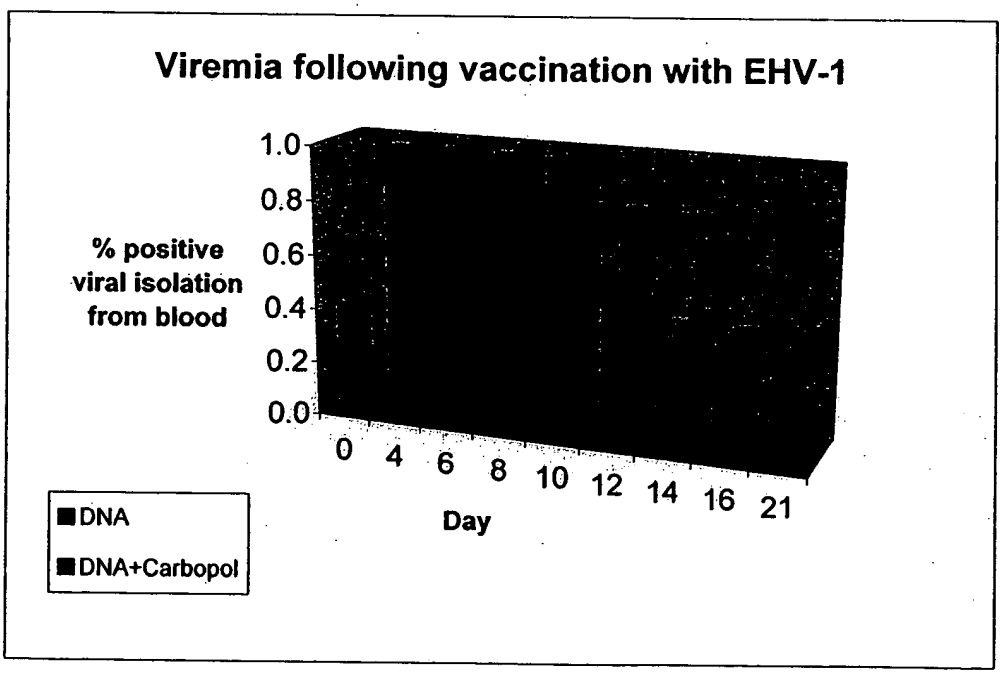
DNA vaccine / EHV1

Vaccine: 3 plasmids expressing gB, gC, gD glycoproteins from EHV-1
Dose: 500µg / ml / plasmid
Adjuvant: Carbopol 3,4 mg / ml
Schedule of immunization: vaccination days 0 and 35, challenge Day 49
Intramuscular, 1 ml

N = 5

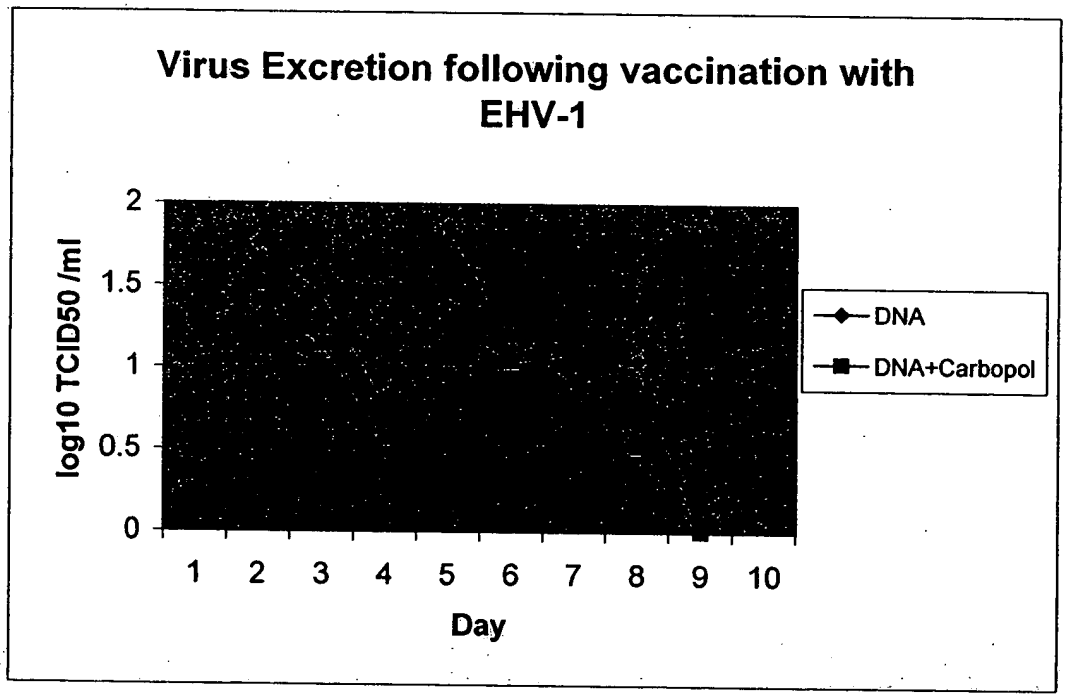
Viremia (% positive viral isolation from blood)

Day [1]	DNA	DNA+Carbopol
0	0.4	0.0
4	1.0	1.0
6	1.0	1.0
8	1.0	1.0
10	1.0	1.0
12	0.6	0.8
14	0.2	0.4
16	0.4	0.4
21	0.4	0.2
Duration (days)	DNA	DNA+Carbopol
Mean	12.4	11.0



Virus excretion (Log10 TCID50 /ml)

Day	DNA	DNA+Carbopol
1	1.26	1.29
2	1.76	1.41
3	1.46	1.14
4	0.79	0.57
5	1.86	1.30
6	1.19	1.04
7	0.92	1.09
8	1.04	0.52
9	0.00	0.00
10	0.32	0.47



Neutralizing antibodies (log10 titer)

Day	DNA	DNA+Carbopol
0	1.31	1.05
14	1.33	1.13
35	1.23	1.35
42	1.27	1.47
49	0.91	1.20
70	2.61	2.75